ACCESSION NUMBER: 92:72472 USPATFULL
TITLE: Halomacrolides and derivatives having immunosuppressive activity
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PATENT ASSIGNEE(S): Merck & Co., Inc., Rahway, NJ, United States (U.S. corporation)

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EXEMPLARY CLAIM: 1,9
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(54) INHIBITOR AGAINST PHOTOSENSITIVITY

(57)Abstract:
PROBLEM TO BE SOLVED: To obtain a preparation having an excellent inhibitor activity against photosensitivity especially when administered externally (percutaneously), by including a specific compound having an immunosuppressive activity as the active ingredient.
SOLUTION: This preparation for external (precutaneous) use for skin, preferably, is prepared by formulating (A) macrolide(s) or analogue(s)/derivatives thereof, cyclosporine A or analogue(s)/derivative(s) thereof, having an immunosuppressive activity as the active ingredient, and (B) an oil, surfactant, perfume, anti-oxidant, UV light-absorber, coloring matter, alcohol, water, moisturizing agent, and/or thickening agent, if necessary. In gradient A is preferably ascomycin, FK506, and/or cycloporine A. Combination of these ingredients affords and additive or synergistic effect on the inhibition agent photosensitivity. The daily dose of the above preparation is preferably 0.1μg- to 10mg-active ingredient/cm2-lesion. It is preferable to administrate the amount divides in 1-4 portions per day.

LEGAL STATUS

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* NOTICES *

1. This document has been translated by computer.So the translation may not reflect the original precisely.
2. **** shows the word which can not be translated.
3.In the drawings, any words are not translated.

CLAIMS

[Claim(s)]
[Claim 1] an immunosuppression operation -- having -- and a macrolides row -- cyclosporin A and its relative -- the tablet for the photodermatosis suppression which comes to contain at least one sort of compounds chosen from a compound group as an active principle
[Claim 2] The tablet of the sake for [that macrolides are ascomycin and] envelopes according to claim 1.

[Translation done.]

DETAILED DESCRIPTION

[Detailed Description of the Invention]
[0001]
[The technical field to which invention belongs] this invention relates to the tablet for photodermatosis suppression used for medicine and a cosmetics science target.
[0002]
[Description of the Prior Art] There is a disorder of exogenous and endogenicity, for example, the foreign photosensitization matter contacts the skin, and the former has in photodermatosis the phototoxic dermatitis and the contact photoallergy nature dermatitis whose symptoms are shown when the beam of light of a fixed field is irradiated by the part or other parts. As hyperesthesia-optica nature disorders other than this, there are various disorders, such as a continued type hyperesthesia-optica reaction (endogenicity) whose symptoms it is concerned and are shown only by irradiation of a beam of light that there is nothing, actinic reticuloid, chronic hyperesthesia-optica nature eczema, and polymorphic light eruption, with a foreign material. (For example, the principle (Photosensitivity Diseases:Principles of Diagnosis and Treatment) of a "daylight hypersensitivity eczema:diagnosis and disposal, Leonard C.Harber and David R.Bickers, B.C.Decker Inc., 1989, reference) . These disorders are chronic intractable disorders which a symptom is discovered and also cause trouble extremely to everyday life also with the beam of light of a minute amount in a patient with an advanced disease.
[0003] Medication of a steroid was conventionally performed for these treatment. Moreover, as a prophylaxis, in order to intercept a beam of light, the application of a sun block was performed. However, it was physically difficult the steroid an operation to be not only weak, but for a side effect to be discovered, and for it to be necessary to continue applying about a sun block that there are no dark circles in the daylight exposure section on the other hand, and to intercept a beam of light perfectly by using continuously. This invention persons proposed chalcone glycoside content physic and a unregulated drug effective in this disorder under such a background (refer to JP,8-20542,A). On the other hand, a certain fixed skin disease has some which originate unusually [an immune system], and also has the attempt which uses an immunosuppresant for the treatment of specific skin disease. For example, using the mass KOMAISHI (Ascomycin) derivative which is the typical medicine which has an immunosuppression operation for the treatment of dermatitis is proposed (the [international public presentation] refer to No. 91/13899 pamphlet). According to this pamphlet, it is suggested that it is effective in dermatitis with an extensive mass KOMAISHI derivative, for example, cutaneous sensitization, atopic dermatitis, the erythema multiforme, the wheal, etc.
[0004]
[Problem(s) to be Solved by the Invention] As mentioned above, this invention persons do not show a side effect, but the chalcone glycoside content medicine for external application which has effect for prevention and treatment of photodermatosis is proposed. however, the further **** turned to the disposal of this disorder when taking the versatility of the nosogeny of photodermatosis into consideration -- the need for a certain agent for envelopes coming to hand still exists -- I will come out
[0005] Therefore, the purpose of this invention is to offer the physic of the sake the tablet for photodermatosis suppression which makes an active principle the compound belonging to different criteria from the aforementioned chalcone glycoside, especially for envelopes, and the tablet for unregulated drugs.
[0006]
[Means for Solving the Problem] This invention persons used the evaluation system (it can be especially regarded as a photodermatosis model) of the effect of a medicine used when developing the above-mentioned chalcone glycoside content tablet, and have screened the compound effective in this evaluation system. Consequently, the specific compound which has an immunosuppression operation found out having higher efficacy to photodermatosis by envelope (or transderma) medication especially.
[0007] in order [therefore,] to solve the above-mentioned technical problem according to this invention -- an immunosuppression operation -- having -- and a macrolides row -- cyclosporin A and its relative -- tablet ** for photodermatosis suppression which comes to contain at least one sort of compounds chosen from a compound group as an active principle is offered
[0008] As for the desirable mode of this invention, the aforementioned tablet is offered as a tablet for envelopes (or for transderma).
[0009] the immunosuppression operation which can be used as an active principle by this invention -- having -- and a

macrolides row -- cyclosporin A and its relative -- as long as a compound is a compound in alignment with the purpose of this invention, it may be what compound of defined within the limits
[0010] More specifically as a typical thing of the aforementioned macrolides Ascomycin which an Actinomyces produces (Arai, T. et al., "Ascomycin, an antifungal antibiotic", J.Antibiotics, Ser.A, 15, 231, 1962) : about the use as the immunosuppresant Refer to the Europe patent application public presentation No. 323865 specification and FK506 (2713 Goto, T. [et al.], "FK506:Historical perspectives", Transplant.Proc., 23: 1991), These analogs and derivatives that were discovered or developed after that by the row can be mentioned.
[0011] Moreover, the cyclosporin A which is the typical compound of another type is the immunosuppresant which an Actinomyces produces, and Kamiichi is carried out as an immunosuppresant which will act on T helper cell specifically in 1983 (Shevach, M. "The effects of Cyclosporin A - the immune system", Ann.Rev.Immunol., 3, 397, 1985). In this invention, the analog and derivative of cyclosporin A can also be used as an active principle.
[0012] In the concrete thing of the aforementioned analog or a derivative Although not limited, ****** No. 510304 [six to], the international public presentation 91st / No. 13899, said -- the 94th / No. 21643 -- said -- the [the 96th / No. 13249, and / this] -- No. 95/4061 the Europe patent application public presentation No. 626385, the international public presentation 94th / No. 21642 -- said -- the 94th / No. 21635 -- said -- the 94th / No. 21634 -- said -- the 93rd / No. 25533 -- said -- the compound indicated by the 93rd / No. 14780 is included
[0013] Also in these, the ascomycin first found out as a production object of a microorganism, FK506, and cyclosporin A are desirable, and especially ascomycin is desirable. Moreover, according to this invention, two or more sorts of above-mentioned compounds can also be used together. For example, according to ascomycin, cyclosporin A, FK506, cyclosporin A, etc., additive or the synergistic effect can be acquired to the depressant action to photodermatosis.
[0014] The tablet of this invention which contains the above-mentioned compound as an active principle has the intention of offer of the tablet of the sake for envelopes (for transderma) as main dosage forms. These concrete dosage forms may be a medicine top or which dosage forms by which daily use on cosmetics science (as the charge of makeup) is carried out, for example, can be a liquid, a milky lotion, a cream, a cartilage, and the poultice.
[0015] the oil content and surfactant which are pharmaceutically permitted besides the aforementioned active principle by the tablet of this invention, perfume, an antioxidant, an ultraviolet ray absorbent, coloring matter, alcohol, water, a moisturizer, a thickening film agent, etc. -- one sort -- or two or more sorts can be added These tablets can be offered by the well-known manufacture method by this work technical field. In this way, although the active principle included in the tablet offered cannot be specified by dosage forms since the optimal amount is changed, the optimal amount could be determined for the example of a tablet specifically mentioned later as reference.
[0016] Although it cannot limit clearly since the dose of the tablet of this invention changes with age, individual differences, condition of disease, etc., the dose of the active principle in the case of generally medicating people reaches 1cm 2 of affected parts, is 1micro g-1mg preferably, and can prescribe 0.1micro per day g-10mg of this amount for the patient in 1 time per or 2 - 4 steps day.
[0017]
[Example] Next, an example is shown and this invention is explained still more concretely. In addition, thereby, this invention is not limited.
[0018] The following examination was carried out in order to clarify effect over the hyperesthesia-optica nature disorder of a tablet at the example this invention of an effect examination.
[0019] The ascomycin according to this invention, FK506, cyclosporin A and the hinney mycin as an example of comparison, auranofin, the indomethacin, and the dexamethasone were dissolved in ethanol by the conventional method, and the skin external application solution was prepared.
[0020] The examining method (11 Ichikawa, H. et al., "Adjuvant-induced persisitent photosensitivity models in guinea pigs", J.Dermatol.Sci., 9, 1- 1995) for a hyperesthesia-optica nature disorder using a continued type photodermatosis model as a measuring method of the curative effect of a medicine was followed.
[0021] First, it is 5mg/ml in concentration, and immunization was suspended in Freund's incomplete adjuvant, and after emulsification, from the weight of 380g, intradermal injection of the dried cell of Mycobacterium BUCHIRIKAMU (Mycobacterium butyricum) was carried out to the regions of neck of a 450g guinea pig, and it performed it with a physiological salt solution. Next, it is the ultraviolet A after applying 0.1ml of 5% ethanol solutions of a benzocaine as quality of contact photoallergy causal agents 10J/cm 2 It irradiated in the amount of energy. Also after (14 days of immunity guidance disposal, and 15 days), application of a benzocaine and irradiation of ultraviolet rays were continuously performed further for five days.
[0022] Each above-mentioned ethanol solution is applied to the regions-of-back skin sheared and shaved 24 days after the first day of immunity guidance disposal, and it is 2 10J/cm after [of an application] 30 minutes. The hyperesthesia-optica reaction was induced by irradiating ultraviolet A. The depressor effect to the hyperesthesia-optica reaction of a medicine was judged by computing the rate of suppression by making into positive control the part which irradiated ultraviolet rays without applying a medicine.
[0023] the judgment of a skin reaction -- a spectrum -- the strength of a skin reaction was measured with the formula color difference meter, and it carried out by examining the depressor effect of the **** matter to a skin reaction The average (E) of the strength of the skin reaction of the part which applied the quality of the specimen was subtracted from the average (C) of the strength of the skin reaction of the positive control part which irradiated ultraviolet A, without applying the quality of the

specimen, and the value which **(ed) by the average (C) of the strength of the skin reaction of a positive control part, and multiplied by 100 was made into the rate of suppression (%).
[0024]
The rate of [(C-E)/C] x100= suppression (%)
A result is summarized in the following table I.
[0025]
[Table 1]
表 I

試験例番号	被検物質	適用量 (μg/cm²)	24時間後の 反応強度(E)	抑制率(%)
1	アスコマイシン	1	0.3	90.6
2	〃	10	0.2	93.8
3	FK506	1	0.3	90.6
4	〃	10	0.2	93.8
5	サイクロスポリンA	10	1.6	50.0
6	〃	100	1.0	31.3
7	ラパマイシン	10	2.6	18.8
8	〃	100	2.7	15.6
9	オーラノフィン	10	3.0	6.3
10	〃	100	3.0	6.3
11	インドメタシン	100	3.2	0.0
12	デキサメタゾン	25	3.1	3.1
	無処置（陽性対照）	-	3.2(C)	

[0026] The tablet used for front Naka and the examples 1-6 of an examination is a tablet of this invention, and the tablet used for these examples 7-12 is a comparison tablet.
[0027] Carrying out each example using the guinea pig of one groups [five] as ******-ed, a test result is the average.
[0028] Next, the example of a tablet according to this invention is shown with the manufacture method below.
[0029]
例1 (軟膏剤)

(1) アスコマイシン		0.1%
(2) プラスチベース	50W	99.9
	計	100.0%

(1) was kneaded to (2) which consists of a liquid paraffin (95%) and polyethylene (5%), reduced pressure deaeration was carried out, and ointment was obtained.
[0030]
Example 2 (cream pharmaceuticals)
A. A cetanol 4.0% Vaseline 7.0 Isopropyl myristate 8.0 Squalane 12.0 Dimethylpolysiloxane 3.0 Glycerol monostearate 2.2 POE(20) sorbitan monostearate 2.8 glycyrrhetinic-acid stearate 0.02 Ethylparaben 0.1 Butylparaben 0.1B. aqueous phase Ascomycin 0.1 1, 3-butylene glycol 7.0 phenoxyethanol 0.2 Ascorbic-acid phosphoric ester magnesium salt 4.0 Purified water Remainder meter While agitating the A phase which carried out the heating dissolution at 70 degrees C at the B phase which

dissolved ascomycin in 1 and 3-butylene glycol 100.0%, added phenoxyethanol and ascorbic-acid phosphoric ester magnesium salt, and was kept at 70 degrees C. It quenched agitating, after performing homomixer processing and making an emulsification particle fine in addition, and the cream was obtained.

[0031]

Example 3 (lotion)

A. FK506 0.5% Ethanol 7.0 Polyoxyethylene (20) oleyl ether 0.5 Methylparaben A 0.05B. glycerol 4.0 1, 3-butylene glycol 4.0 Citric acid 0.01 Citric-acid soda 0.1 Purified water Remainder Total In addition to the B phase melted to the purified water, the A phase melted to ethanol 100.0% is solubilized and filtered. The lotion was obtained.

[0032]

例4 (パスタ剤)

サイクロスポリンA	2.0%
酸化亜鉛	30.0
デンプン	30.0
白色ワセリン	38.0
計	100.0%

After being on a water bath, melting a part of white vaseline and adding cyclosporin A, the zinc oxide and starch which carried out **** through were kneaded, and the residual white vaseline was added, and it kneaded together enough, and manufactured as the quality of all being equal.

[0033]

[Effect of the Invention] According to this invention, the tablet especially for envelopes suitable for the disposal of the new photodermatosis which hardly shows a side effect is offered. Since these tablets show higher efficacy to prevention and treatment of photodermatosis, they can be used in the field of physic and a unregulated drug.

[Translation done.]

conjunction with the primary treating agent include administration of agents for the treatment of psoriasis, such as 5-LO inhibitors (e.g., Lonapalene, Zileuton, epocarbazolin-A, and the like), 5-LO/CO inhibitors (e.g., Tenidap), angiogenesis inhibitors (e.g., platelet factor 4), anticancer antibiotic, anti-inflammatory cytochrome P450 oxidoreductase inhibitors, antiproliferative compounds (e.g., Zyn-Linker), arachidonic acid analogues, arachidonic acid antagonists (e.g., Lonopalene. triamcinolone acetonide with penetration enhancer Azone, betamethasone dipropionate steroid wipe, Halobetasol propionate, ultravate, Halometasone, Sicorten, and the like), beta-glucan receptor antagonists, betamethasone steroid wipes, calcium metabolic moderators (e.g., Tacalcitol, Bonealfa, Calcipotriol, Dovonex, and the like), CD4 binding inhibitors, cell adhesion inhibitors (e.g., selectin inhibitor), cellular aging inhibitors (e.g., Factor X), corticosteroids (e.g., Halobetasol propionate, ultravate, Halometasone, Sicorten, and the like), dihydrofolate reductase inhibitors (e.g., dichlorobenzoprim, methotrexate, methotrexate in microsponge delivery system, and the like), E-selectin inhibitors, endogenous active form of vitamin D.sub.3 (e.g., Calcitriol), fibroblast growth factor antagonists (e.g., Saporin mitotoxin, Steno-Stat, and the like), fumagillin analogues, G-proteins and signal transduction compounds, gel formulations for acne (e.g., nicotinamide, Papulex, and the like), growth hormone antagonists (e.g., Octreotide, Sandostatin Lanreotide, angiopeptin, Somatuline, and the like), humanized antibodies (e.g., anti-CD4 antibody), hydroorotate dehydrogenase inhibitors (e.g., Brequinar sodium, bipenquinate, and the like), ICAM-1 inhibitors, IL-1 and other cytokine inhibitors (e.g., Septanil), IL-1 converting ezyme inhibitors, IL-1 receptor antagonists (e.g., Antril), IL-2 antagonists (e.g., Tacrolimus, Prograf, **FK -506**, and the like), IL-2 receptor-targeted fusion toxins, IL-8 receptors, immunostimulants (e.g., Thymopentin, Timunox, and the like), immunosuppressants (e.g., cyclosporine, Sandimmune, anti-CD11, Tacrolimus, Prograf, **FK-506**, FK-507, and the like), leukotriene antagonists, leukotriene B4 antagonists, leukotriene synthesis inhibitors, lipase clearing factor inhibitors (e.g., 1-docosanol, lidakol, and the like), lipid encapsulated reducing agent (e.g., Dithranol), liposomal gel (e.g., Dithranol), lithium succinate ointments (e.g., lithium salts, Efalith, and the like), octapeptide somatostatin analogues (e.g., Lanreotide, angiopeptin, Somatuline, and the like), PKC inhibitors, phospholipase A2 compounds, photodynamic anticancer agents (e.g., 5-aminolevulinic acid), photodynamic therapies (e.g., benzoporphyrin derivatives, synthetic chlorins, synthetic porphyrins, and the like), PKC inhibitors (e.g., Safingol, Kynac, and the like), platelet activating factor antagonists, platelet aggregation inhibitors (e.g., CPC-A), prostaglandin agonists (e.g., eicosapentaenoic acid+gamma-linolenic acid combination, Efamol Marine, and the like), protein kinase C (PKC) inhibitors, protein synthesis antagonists (e.g., Calcitriol, Namirotene, and the like), purine nucleoside phosphorylase inhibitors, radical formation agonists (e.g., benzoporphyrin derivatives), recombinant antileukoproteinases, retinoids, retinoid derivatives, rapamycin binding proteins (FKBP) (e.g., immunophilins), second generation monoaromatic retinoids (e.g., Acitretin, Neotigason, and the like), soluble IL-1, IL-4 and IL-7 receptors, somatostatin analogues (e.g., Octreotide, Sandostatin, and the like), superoxide dismutase, thymidylate synthase inhibitors, transglutaminase inhibitors, tyrphostin EGF receptor kinase blockers, VCAM-1 inhibitors, and the like.

DETD Moisturizers contemplated for use in the above-described **topical** formulations include occlusive moisturizers, such as, for example, **hydrocarbon** oils and waxes, petroleum jelly, silicone oils, silicone derivatives, vegetable and animal fats, cocoa butter, mineral oil, fatty acids, fatty alcohols, lanolin, phospholipids, and the like; humectants, such as, for example, glycerin, honey, **lactic** acid, **sodium lactate**, ceramide, **urea**, propylene glycol, sorbitol, pyrrolidone carboxylic acid,

glycolic acid, gelatin, vitamins, proteins, and the like; hydrophilic matrices, such as, for example, hyaluronic acid, colloidal oatmeal, and the like; essential fatty acids (e.g., Dermasil), elastin, niosomes, and the like.

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INVENTOR(S): Lai, Ching-San, Encinitas, CA, United States
Vassilev, Vassil, San Diego, CA, United States
PATENT ASSIGNEE(S): Medinox Inc., San Diego, CA, United States (U.S. corporation)

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